

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
3 June 2004 (03.06.2004)

PCT

(10) International Publication Number
WO 2004/045574 A1

(51) International Patent Classification⁷: **A61K 7/48**

(21) International Application Number:
PCT/US2003/013489

(22) International Filing Date: 29 April 2003 (29.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/299,161 19 November 2002 (19.11.2002) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PRODUCTS AND METHODS FOR MAINTAINING OR INCREASING CERAMIDE LEVELS IN SKIN

(57) Abstract: Disclosed are methods and products such as wet wipes and absorbents capable of providing a skin health benefit when utilized in the intended fashion. More specifically, the products described herein comprise an agent, such as a botanical extract, which is capable of increasing the activity of sphingomyelinase according to a Sphingomyelinase Activity Screening Test and/or decreasing the activity of ceramidase according to a Ceramidase Activity Screening Test. By increasing the activity of sphingomyelinase and/or decreasing the activity of ceramidase, the agents in combination with the products described herein are able to maintain or increase the level of ceramides in the skin leading to improved skin health.

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PRODUCTS AND METHODS FOR MAINTAINING OR
INCREASING CERAMIDE LEVELS IN SKIN

BACKGROUND OF THE INVENTION

5 The present invention relates to products and methods for maintaining or increasing the intracellular concentration of ceramides. More particularly, the present invention relates to the use of certain agents, such as botanical extracts, in wipes and absorbent products to maintain or
10 increase intracellular ceramide concentrations. Intracellular ceramide concentrations are maintained or increased in the present invention by introducing one or more agents capable of increasing the activity of sphingomyelinase and/or decreasing the activity of ceramidase.

15 Ceramide (N-acylsphingosine) is a lipid metabolite and is an important intracellular messenger which is released inside a cell within a few hours of stimulation with various agents. Ceramide is regarded as a second messenger in the context of the sphingomyelin signal transduction pathway, and
20 fulfills an important role in the moisturizing mechanism and barrier mechanism of skin. Ceramides are released by sphingomyelin as a result of the enzymatic effect of sphingomyelinases, which are forms of phospholipase C specific for sphingomyelin. Inside the cells, ceramide can
25 influence growth and differentiation, regulate protein secretion, induce DNA fragmentation and apoptosis, and increase the synthesis and secretion of cytokines. Hydrolysis of sphingomyelin occurs rapidly after exposure of the cells to exogenous sphingomyelinase or to agonists which
30 activate endogenous sphingomyelinases.

 The importance of ceramides in the skin metabolism and health is well documented. The main cellular constituents of the epidermis are keratinocytes, melanocytes, Langerhans cells, fibroblasts, endothelial cells and macrophages. The

intracellular space consists mainly of neutral lipids, glycoproteins, protein degradation products, desmosomes, active enzymes, products of sebaceous glands, and ceramides. As long as this brick and mortar structure is intact, the skin is endowed with both a protective layer and a selectively permeable filter.

During the differentiation process of the epidermis, which starts with cell division in the basal layer and ends with the death of keratinocytes and the development of the lipid barrier, the cells modify their lipid synthesis capability. The result is that the basal layer of the epidermis is characterized by phospholipids and cholesterol, whereas the outermost layer is characterized by cholesterol, free fatty acids and ceramides. The lipids of the horny layer, the main component of which consists of sphingolipids, play a crucial role in maintaining the permeability barrier of the epidermis to water. The sphingolipids are exuded from the lamellar bodies of the granular cells of the epidermis. Ceramides, which make up almost 50% of the horny layer of skin, are the main polar lipids of the horny layer and play a fundamental role in the barrier function of the skin against water leakage in cell adhesion and in the differentiation of the epidermis, as mentioned above.

Like the appearance of the surface of the skin, its functional properties also undergo changes with aging. Aging skin is characterized by a reduced water content in the horny layer associated with reduced transdermal leakage of water. It has been shown that ceramide concentration decreases with age, and this decrease may be responsible for the dehydration of the skin which is observed in the course of aging. In addition, abnormal ceramide levels (deficiencies) have been detected in atopic eczema, dermatosis and dermatitis, atopic dermatitis and psoriasis.

In addition to age, other external factors can reduce the amount of ceramides present in the skin and lead to skin irritation problems. For example, the enzyme ceramidase can degrade ceramides to sphingosine and free fatty acids upon
5 contact with ceramides. Ceramidase is present in skin in certain layers where it performs a beneficial conversion function. However, when ceramidase is introduced onto skin from an external source such as bacteria (bacterial ceramidases) present in feces or nasal secretions, the
10 ceramidase can degrade ceramides as mentioned above thereby reducing the intracellular concentration of ceramides and leading to dry, cracked skin.

In light of the foregoing, it is useful to maintain high levels of ceramides in the skin to maintain and promote
15 healthy skin. As such, it would be advantageous to produce personal care products, such as wet wipes and absorbent care products, capable of maintaining or increasing the levels of ceramides in the skin. Because controlling the ceramide levels in the skin by the addition of natural ceramides is
20 not practical due to the enormous expense of the purified lipid, there continues to be a need for economical products containing agents capable of maintaining or increasing the levels of ceramides in the skin.

25 SUMMARY OF THE INVENTION

The present invention relates to products and methods for improving skin health by maintaining or increasing the concentration of intracellular ceramides. More specifically, the present invention relates to products such as wet wipes
30 and absorbent articles containing agents which are capable of improving the health of skin they contact during normal usage by maintaining or increasing the intracellular concentration of ceramides through various mechanisms.

The products of the present invention may comprise an agent, such as a botanical extract, for increasing sphingomyelinase activity for the production of ceramides by at least about 100%. In one embodiment, the sphingomyelinase activity increasing agent increases sphingomyelinase activity by at least about 100% as determined by a SAST Sphingomyelinase Activity Screening Test set forth herein. Because sphingomyelinase activity is required for the production of intracellular ceramides, an increase in such enzymatic activity results in increased ceramide levels. Furthermore, the products of the present invention may comprise a ceramidase activity decreasing agent for decreasing ceramidase activity by at least about 50%. In one embodiment, the ceramidase activity decreasing agent decreases ceramidase activity by at least about 50% as determined by a CAST Ceramidase Activity Screening Test set forth herein. Because ceramidases, such as bacterial ceramidases present on the skin, can degrade ceramides, a reduction in ceramidase activity reduces the amount of ceramides destroyed. By significantly increasing sphingomyelinase activity and/or decreasing ceramidase activity, the agents described herein significantly improve the health of skin by maintaining or increasing the level of ceramides in the skin.

Briefly, therefore, the present invention is directed to a wipe for improving skin health comprising a fibrous wipe substrate and a sphingomyelinase activity increasing agent for increasing sphingomyelinase activity for the production of ceramides by at least about 100%.

The present invention is further directed to a wipe for improving skin health comprising a fibrous wipe substrate and a ceramidase activity decreasing agent for decreasing ceramidase activity by at least about 50%.

The present invention is further directed to a wipe comprising a fibrous wipe substrate and a sphingomyelinase activity increasing agent for increasing sphingomyelinase activity for the production of ceramides by at least about 100% and a ceramidase activity decreasing agent for decreasing ceramidase activity by at least about 50%.

The present invention is further directed to a method for increasing the intracellular concentration of ceramides. The method comprises contacting skin with a sphingomyelinase activity increasing agent for increasing sphingomyelinase activity for the production of ceramides by at least about 100%.

Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, it has been discovered that certain agents, such as certain botanical extracts, can be utilized in common products to maintain or increase the concentration of ceramides in skin and thereby improve skin health. Some of the agents described herein are capable of increasing sphingomyelinase activity by at least about 100% according to a SAST Sphingomyelinase Activity Screening Test set forth herein. By significantly increasing sphingomyelinase activity, the rate at which ceramides are produced is increased leading to a higher intracellular concentration of ceramides. Additionally or alternatively, the personal care products of the present invention can also improve the health of skin by comprising an agent capable of decreasing ceramidase activity by at least about 50% according to a CAST Ceramidase Activity Screening Test set forth herein. By reducing the activity of ceramidase at or near the skin surface, the level of destruction of ceramides is reduced resulting in a higher concentration of active

ceramide compounds. Furthermore, it has been discovered that certain organic and inorganic cofactors can be used in combination with one or more of the agents described herein to provide additional benefits to the skin by further
5 stimulating sphingomyelinase to increase the production of ceramides.

The personal care products of the present invention contain at least one agent, such as a botanical extract, which is capable of improving the health of skin contacted by
10 the personal care product during normal use. Numerous personal care products can be used with the agents described herein in accordance with the present invention to improve the skin of the user. For example, one or more of the agents and/or cofactors described herein can be used in combination
15 with wipes, such as wet wipes, hand wipes, face wipes, cosmetic wipes, household wipes, industrial wipes, dry wipes and the like, to improve the health of the skin by maintaining or increasing the ceramide level therein. Materials suitable for the substrate of the wipe are well
20 known to those skilled in the art, and are typically made from a fibrous sheet material which may be either woven or nonwoven. For example, the wipes incorporating the agents described herein to improve skin health may include nonwoven fibrous sheet materials which include meltblown, coform, air-
25 laid, bonded-carded web materials, hydroentangled materials, and combinations thereof. Such materials can be comprised of synthetic or natural fibers, or a combination thereof. Typically, wipes define a basis weight of from about 25 to about 120 grams per square meter and desirably from about 40
30 to about 90 grams per square meter.

In a particular embodiment, the wipes incorporating the agents described herein comprise a coform basesheet of polymeric microfibers and cellulosic fibers having a basis weight of from about 60 to about 80 grams per square meter

and desirably about 75 grams per square meter. Such coform basesheets are manufactured generally as described in U.S. Patent No. 4,100,324, which is incorporated by reference. Typically, such coform basesheets comprise a gas-formed
5 matrix of thermoplastic polymeric meltblown microfibers, such as, for example, polypropylene microfibers, and cellulosic fibers, such as, for example, wood pulp fibers.

The relative percentages of the polymeric microfibers and cellulosic fibers in the coform basesheet can vary over a
10 wide range depending upon the desired characteristics of the wet wipes. For example, the coform basesheet may comprise from about 20 to about 100 weight percent, desirably from about 20 to about 60 weight percent, and more desirably from about 30 to about 40 weight percent of the polymeric
15 microfibers based on the dry weight of the coform basesheet being used to provide the wipes.

Alternatively, the wipes incorporating the agents described herein comprise a composite which includes multiple layers of materials. For example, the wipes may include a
20 three-layer composite which includes an elastomeric film or meltblown layer between two coform layers as described above. In such a configuration, the coform layers may define a basis weight of from about 15 to about 30 grams per square meter and the elastomeric layer may include a film material such as
25 a polyethylene metallocene film.

As mentioned above, one type of wipe suitable for use in combination with the agents described herein to improve skin health include wet wipes which contain a liquid solution or formulation. The amount of solution contained within each
30 wet wipe may vary depending upon the type of material being used to provide the wet wipe, the type of solution being used, the type of container being used to store the wet wipes, and the desired end use of the wet wipes. Generally, each wet wipe can contain from about 150 to about 600 weight

percent and desirably from about 250 to about 450 weight percent solution based on the dry weight of the wipe for improved wiping. In a particular aspect, wherein the wet wipes are made from a coform material comprising from about
5 30 to about 40 weight percent polymeric microfibers based on the dry weight of the wipe, the amount of solution contained within the wet wipe is from about 300 to about 400 weight percent and desirably about 330 weight percent based on the dry weight of the wet wipe. If the amount of solution is
10 less than the above-identified range, the wet wipe may be too dry and may not adequately perform. If the amount of solution is greater than the above-identified range, the wet wipe may be oversaturated and soggy and the solution may pool in the bottom of the container holding the wet wipes.

15 In another embodiment, the personal care products which comprise one or more of the agents described herein for improving skin health can include absorbent personal care products such as diapers, training pants, adult incontinence garments, feminine napkins, paper towels, tampons, breast
20 pads, interlabial pads, facial tissue, wound management products, and bath tissue. Such absorbent products are commonly utilized for absorbing various fluids including bodily fluids such as blood, menses, nasal secretions, feces, and urine. Materials and methods for making such absorbent
25 products are well known to those skilled in the art. When utilized in their intended manner, the absorbent personal care products including the agent or agents described herein contact the skin such that the agent can interact with the naturally occurring skin compounds and improve the health of
30 the skin.

In one embodiment of the present invention, an agent capable of increasing the activity of the enzyme sphingomyelinase is introduced into or onto a personal care product to improve the health of skin contacted by the

personal care product by increasing ceramide production in the skin via the pathway described above. As previously mentioned, sphingomyelinase is an enzyme which hydrolyses the lipid sphingomyelin, a phospholipid component of cell
5 membranes, to produce ceramide. As used herein the phrase "increasing the activity of the enzyme sphingomyelinase" and similar phrases mean that the enzymatic activity of sphingomyelinase on sphingomyelin is increased in the presence of the agent, as compared to the activity of
10 sphingomyelinase on sphingomyelin in the absence of the agent. By introducing one or more of the agents described herein into or onto a personal care product, the agent(s) contacts the skin during use and can interact with the naturally occurring sphingomyelinase to increase the
15 sphingomyelinase activity. In addition to interacting with naturally occurring sphingomyelinase, the agent can also interact with sphingomyelinase which may be present in exudates, such as feces or nasal secretions, to facilitate ceramide production at or near the skin surface. The
20 increased sphingomyelinase activity results in an increased hydrolysis of sphingomyelin and the production of ceramides through *in situ* reactions on or near the skin surface, which is beneficial and improves skin health as discussed above.

Preferably, the agent, or combination of agents
25 introduced into or onto the personal care product, is capable of increasing sphingomyelinase activity by at least about 100%, more preferably at least about 200%, still more preferably at least about 300%, and most preferably at least about 400%, as compared to the sphingomyelinase activity in
30 the absence of the agent. In one embodiment, the agent or combination of agents introduced into or onto the personal care product, is capable of increasing sphingomyelinase activity by at least about 100%, more preferably at least about 200%, still more preferably at least about 300%, and

most preferably at least about 400% as determined by a SAST Sphingomyelinase Activity Screening Test set forth herein. Such increases in sphingomyelinase activity can result in increased intracellular and extracellular levels of

5 ceramides, which improves skin health. The sphingomyelinase activity increasing agent is preferably for increasing sphingomyelinase activity by at least about 100% as noted above. While this is the purpose and capability of the agent under many circumstances, it is noted that under certain

10 conditions of application and skin condition, the actual increase in activity experienced on the skin may be other than at least about 100% even though the agent is for increasing such activity by at least about 100%.

15 SAST Sphingomyelinase Activity Screening Test

Agents, such as botanical extracts and related compounds, for example, are tested for their ability to increase the activity of sphingomyelinase in a sphingomyelinase/sphingomyelin-containing system. An

20 increase in the activity of sphingomyelinase results in an increase in the hydrolysis of sphingomyelin and an increased production of ceramide. The Sphingomyelinase Activity Screening Test to determine the efficacy of an agent is completed as follows:

25

Preparation of Testing Solutions:

Step 1: Preparation of Testing Solution Comprising Sphingomyelinase, Sphingomyelin, and Agent: Combine the following to prepare a 100 microliter test solution: (1) 10

30 microliters of agent (such as a botanical extract, for example) where the agent is an aqueous solution or oil (if the agent is a powder or solid, prepare 10 microliters of a 0.1 microgram/milliliter solution by dissolving the appropriate amount of powder or solid in Phosphate Buffered

Saline, pH = 7.4); (2) 10 microliters of a 0.1 microgram/milliliter sphingomyelinase (Catalogue No. S7651, Sigma Chemical, St. Louis, Mo. (or equivalent)) in Phosphate Buffered Saline, pH = 7.4, solution; (3) 10 microliters of a
5 250 microgram/milliliter BODIPY FL C5-Sphingomyelin (Molecular Probes, Eugene, Or. (or equivalent)) in Phosphate Buffered Saline, pH = 7.4, solution; and (4) 70 microliters of Phosphate Buffered Saline, pH = 7.4.

Step 2: Preparation of Control Testing Solution

10 Comprising Sphingomyelinase and Sphingomyelin: Combine the following to prepare a 100 microliter test solution: (1) 10 microliters of a 0.1 microgram/milliliter sphingomyelinase in Phosphate Buffered Saline, pH = 7.4, solution; (2) 10 microliters of a 250 microgram/milliliter BODIPY FL C5-
15 Sphingomyelin in Phosphate Buffered Saline, pH = 7.4, solution; and (3) 80 microliters of Phosphate Buffered Saline, pH = 7.4.

Step 3: Preparation of Control Testing Solution

Comprising Sphingomyelin: Combine the following to prepare a
20 100 microliter test solution: (1) 10 microliters of a 250 microgram/milliliter BODIPY FL C5 Sphingomyelin in Phosphate Buffered Saline, pH = 7.4, solution; and (2) 90 microliters of Phosphate Buffered Saline, pH = 7.4.

Step 4: Preparation of Control Testing Solution

25 Comprising Agent and Sphingomyelin: Combine the following to prepare a 100 microliter test solution: (1) 10 microliters of agent where the agent is an aqueous solution or oil (if the agent is a powder or solid, prepare 10 microliters of a 0.1 microgram/milliliter solution by dissolving the
30 appropriate amount of powder or solid in Phosphate Buffered Saline, pH = 7.4); (2) 10 microliters of a 250 microgram/milliliter BODIPY FL C5 Sphingomyelin in Phosphate Buffered Saline, pH = 7.4, solution; and (3) 80 microliters of Phosphate Buffered Saline, pH = 7.4.

Assay:

Step 1: Shake each of the four test solutions for 30 minutes on a laboratory shaker (e.g. S/P Vortrex-Genie; Deerfield, Il. at a setting of about 6) at 25°C to thoroughly mix each testing solution and allow chemical interaction and reaction between the testing mixture components.

Step 2: Add 1 milliliter of a 2:1 (by volume) mixture of chloroform:methanol to each testing solution to stop the chemical reactions. After the addition of the chloroform:methanol mixture, each testing solution is vortexed (e.g. S/P Vortrex-Genie; Deerfield, Il. at a setting of about 6) for a period of time of about 1 minute to ensure that the chloroform:methanol mixture is thoroughly distributed throughout the testing mixture.

Step 3: Remove 0.8 milliliters of solution from the organic phase of each testing solution and introduce the removed solution into a thin layer chromatography vial for further analysis.

Thin Layer Chromatography Procedure:

Step 1: Introduce 5 microliters of a testing solution onto a thin layer chromatography plate, such as a high performance thin layer chromatography silica gel 60 plate (MERCK, Damstadt, Germany), or similar plate. The spotting of the testing solution onto the plate may be done with a CAMAG Auto TLC Sampler 4 (Muttens, Switzerland) for example, or similar device.

Step 2: Develop each testing solution by introducing a 90:20:0.5 (by volume) chloroform:methanol:ammonium hydroxide mixture onto each plate and allowing the mixture to run to a length of 8 centimeters.

Step 3: Quantify the fluorescent cleavage products on the thin layer chromatography plates by image analysis using an Alpha Innotech Flourchem Plate Imaging System (San Leandro, Ca), or similar system. Each plate typically

contains a maximum of ten test samples, three positive control samples (substrate and sphingomyelinase) and one negative control sample (substrate and no enzyme). The plates were imaged by illuminating with a UV light source (364 nm) and a digital image was taken through a 585 nm barrier filter with the Flourchem Imager. All fluorescent bands are analyzed using the Flourchem image analysis software and the brightness for each band determined. The Flourchem software determined the Integrated Density Value (IDV) and the Area (pixels) for each fluorescent band. From this information, a Brightness value is calculated by the Fluorchem software. The following calculation is used:

$$\text{Brightness} = \text{IDV}/\text{AREA}$$

where the IDV is the sum of all of the pixel values, AREA is the size (in pixels) of the region enclosed by a box of 2000-2500 pixels in size. To calculate the effect of the compounds on enzyme activity, the negative control brightness is first subtracted from all of the samples. Then the test compound band on a plate is divided by the average value of the three positive control bands for the same plate. A value above 1 indicates a sphingomyelinase enhancer, a value below 1 indicates an inhibitor.

Suitable agents for use in combination with the personal care products described herein to increase the activity of sphingomyelinase by at least about 100% to ultimately produce an increased amount of intracellular ceramides include both botanical extracts and other compounds. Specifically, it has been found that the following agents increase sphingomyelinase activity as determined by the Sphingomyelinase Activity Screening Test described herein by at least about 100% and are suitable for use in accordance with the present invention: Sedaplant Richter, Chlorella,

Hexaplant Richter, Lavender, Marigold (Calendula), Gotu Kola
PE 4:1, Spirulina, Chamomile CL, Harpagophytum (Devil's
Claw), Dragoderm, Phytoplenolin, Aloe Ferox HS, Sea Parsley
Extract, Butcher's Broom HS, American Ginseng, Microat afa
5 Complex, and Actiphyte of Japanese Green Tea Conc. Preferred
agents are Chlorella, Lavender, Spirulina, Dragoderm, ---
Phytoplenolin, Aloe Ferox HS, and American Ginseng.

When present on a dry wipe substrate or on an absorbent
product, the agent for increasing the activity of
10 sphingomyelinase is present in an amount of from about 0.01%
(by weight of the treated substrate or product) to about 50%
(by weight of the treated substrate or product), preferably
from about 0.01% (by weight of the treated substrate or
product) to about 10% (by weight of the treated substrate or
15 product). When present as part of the liquid formulation of
a wet wipe, the agent is present in an amount of from about
0.01% (by total weight of the liquid formulation) to about
50% (by total weight of the liquid formulation), more
preferably from about 0.01% (by total weight of the liquid
20 formulation) to about 10% (by total weight of the liquid
formulation), and most preferably from about 0.01 % (by total
weight of the liquid formulation) to about 10% (by total
weight of the liquid formulation).

In another embodiment of the present invention, an agent
25 capable of decreasing the activity of the enzyme ceramidase
is introduced into or onto a personal care product to improve
the health of skin contacted by the personal care product by
maintaining or increasing the amount of intracellular and
extracellular ceramides. As mentioned above, ceramidase is
30 an enzyme that can destroy ceramides. Although ceramidase,
which is naturally present in skin, performs a valuable,
necessary function in some layers of the skin, ceramidases
introduced onto the skin's surface or into the upper layers
of the skin from external sources, such as bacterial

ceramidases, which can be present in fecal matter, for example, can destroy ceramides and lead to various skin problems as discussed above. As used herein, the phrase "decreasing the activity of the enzyme ceramidase" means that the enzymatic activity of ceramidase is decreased in the presence of the agent as compared to the enzymatic activity of ceramidase in the absence of the agent. By introducing the agents described herein into or onto a personal care product, the agent contacts the skin during use and can interact with ceramidases deposited thereon and reduce the enzymatic activity of the ceramidases. This results in a decrease in destruction of the ceramides.

The agent, or combination of agents, introduced into or onto the personal care product preferably reduces the enzymatic activity of ceramidase by at least about 50%, more preferably at least about 75%, and most preferably at least about 90% as compared to the ceramidase activity in the absence of the agent. In one embodiment, the agent or combination of agents, introduced into or onto the personal care product preferably reduces the enzymatic activity of ceramidase by at least about 50%, more preferably at least about 75%, and most preferably at least about 90% as compared to the ceramidase activity in the absence of the agent as determined by a CAST Ceramidase Activity Screening Test set forth herein. The ceramidase activity reducing agent is preferably for decreasing ceramidase activity by at least about 50% as noted above. While this is the purpose and capability of the agent under many circumstances, it is noted that under certain conditions of application and skin condition, the actual decrease in activity experienced on the skin may be other than at least about 50% even though the agent is for decreasing such activity by at least about 50%.

CAST Ceramidase Activity Screening Test

Agents, such as botanical extracts and related compounds, for example, are tested for their ability to decrease the activity of ceramidase in a ceramidase/ceramide system. A decrease in the activity of ceramidase results in an increase in the level of ceramides. The Ceramidase Activity Screening Test is completed as follows:

Preparation of Testing Solutions:Step 1: Preparation of Testing Solution Comprising

10 Ceramidase (Fecal Extract), Agent, and Ceramide: Combine the following to prepare a 100 microliter test solution: (1) 10 microliters of agent where the agent is an aqueous solution or oil (if the agent is a powder solid, prepare 10 microliters of a 0.1 microgram/milliliter solution by
15 dissolving the appropriate amount of powder or solid in Phosphate Buffered Saline, pH = 7.4); (2) 10 microliters of infant fecal extract in Phosphate Buffered Saline, pH = 7.4 prepared by extracting 1 gram of infant feces in 9 mL of Phosphate Buffered Saline, pH = 7.4, and vortexing the
20 extraction for about 2 minutes followed by centrifugation to remove any solids; (3) 10 microliters of 250 microgram/milliliter C5 ceramide in Phosphate Buffered Saline, pH = 7.4; and (4) 70 microliters of Phosphate Buffered Saline, pH = 7.4.

Step 2: Preparation of Control Testing Solution

25 Comprising Ceramidase and Ceramide: Combine the following to prepare a 100 microliter test solution: (1) 10 microliters of infant fecal extract in Phosphate Buffered Saline, pH = 7.4; (2) 10 microliters of 250 microgram/milliliter BIODIPY
30 FL C5 ceramide (Molecular Probes, Eugene, Wa.) in Phosphate Buffered Saline, pH = 7.4; and (3) 80 microliters of Phosphate Buffered Saline, pH = 7.4.

Step 3: Preparation of Control Testing Solution

Comprising Ceramide: Combine the following to prepare a 100

microliter test solution: (1) 10 microliters of 250 microgram/milliliter BIODIPY FL C5 ceramide in Phosphate Buffered Saline, pH = 7.4; and (2) 90 microliters of Phosphate Buffered Saline, pH = 7.4.

5 Assay:

Step 1: Allow each testing solution to remain static at 25°C for 18 hours to allow interaction and reaction between the Testing Solution components.

Step 2: Add 200 microliters of a 2:1 (by volume) mixture of chloroform:methanol to each testing solution to stop the chemical reactions. After the addition of the chloroform:methanol mixture, each of the testing solutions is vortexed for a period of about 1 minute to ensure that the chloroform:methanol mixture is thoroughly distributed throughout the testing mixture.

Step 3: Remove 0.8 milliliters of solution from the organic phase of each testing solution and introduce the removed solution into a thin layer chromatography vial for further analysis.

20 Thin Layer Chromatography Procedure:

Step 1: Introduce 10 microliters of a testing solution onto a thin layer chromatography plate, such as a high performance thin layer chromatography silica gel 60 plate as described above.

Step 2: Develop each testing solution by introducing a 90:20:0.5 (by volume) chloroform:methanol:ammonium hydroxide mixture onto each plate and allowing the mixture to run to a length of 8 centimeters.

Step 3: Illuminate each plate with a 364 nanometer light source and take pictures with a suitable camera, such as a digital Kodak DC 40. The digital image is transferred as a TIFF file to the Alpha Innotech Flourchem Plate Imaging System and analyzed as described above with similar positive (substrate and ceramidase) and negative (substrate and no

enzyme) controls. A value above 1 indicates a ceramidase enhancer and a value below 1 indicates an inhibitor.

Suitable agents for use in combination with the personal care products described herein to decrease the activity of ceramidase by at least about 50% to ultimately maintain or increase the amount of ceramides in the skin include both botanical extracts and other compounds. Specifically, it has been found that the following agents decrease ceramidase activity as determined by the Ceramidase Activity Screening Test described herein by at least about 50% and are suitable for use in accordance with the present invention: Dragoderm, Ceramide Complex CLR (P), Green Tea HS-Chilowt, Comfrey Leaves Extract, Hydrolyzed Soy Protein, Glycoderm, Aloe Gel 1:1 Decolorized, American Ginseng, Aloe Ferox HS, and Phytoplentin.

When present on a dry wipe substrate or on an absorbent product, the agent for decreasing the activity of ceramidase is present in an amount of from about 0.01% (by weight of the treated substrate or product) to about 50% (by weight of the treated substrate or product), preferably from about 0.01% (by weight of the treated substrate or product) to about 10% (by weight of the treated substrate or product). When present as part of the liquid formulation of a wet wipe, the agent is present in an amount of from about 0.01% (by total weight of the liquid formulation) to about 50% (by total weight of the liquid formulation), more preferably from about 0.01% (by total weight of the liquid formulation) to about 10% (by total weight of the liquid formulation).

Without being bound to a particular theory, it appears that the agents described herein for reducing the activity of the enzyme ceramidase accomplish this in one of two ways, or through a combination of both. First, the agents may actually be downregulating the production of ceramidase from the external source, which may be bacteria. By interacting

with the bacteria and downregulating, or turning off or reducing ceramidase production, the amount of ceramides destroyed by the ceramidase enzyme is reduced as the concentration of ceramidase is decreased. Alternatively, or
5 in combination with downregulation, the agent(s) may be chemically interacting with the ceramidase molecules and blocking or binding one or more active sites on the enzyme such that the ceramidase is no longer capable, or at least much less capable, of reacting with and destroying ceramides.
10 Although this mechanism alone does not reduce the overall concentration of ceramidase on or near the skin's surface, it does effectively prevent the destruction of ceramides by reducing the ceramidase activity.

In an alternative embodiment of the present invention, a
15 single agent can be introduced into or onto a personal care product to produce a dual effect; that is, the agent acts to increase sphingomyelinase activity and decrease ceramidase activity simultaneously. For example, DragoderM has been shown to increase sphingomyelinase activity by more than 300%
20 as determined by the SAST Sphingomyelinase Activity Screening Test set forth herein and has also been shown to decrease ceramidase activity by at least about 90% as determined by the CAST Ceramidase Activity Screening Test set forth herein. As such, when DragoderM is introduced into or onto a personal
25 care product, it produces the dual effect of not only increasing sphingomyelinase activity on the skin to ultimately produce an increased level of ceramides, but also decreases the destruction of ceramides on the skin by decreasing the activity of ceramidase. Thus, DragoderM
30 provides a dual benefit which is highly desirable. Along with DragoderM, Aloe Ferox HS, American Ginseng, and Phytophenolin have been shown to not only increase sphingomyelinase activity, but also decrease ceramidase activity.

In a further embodiment of the present invention, a combination of agents can be utilized to produce the dual effect of increasing sphingomyelinase activity while decreasing ceramidase activity to produce an increased level of ceramides in the skin for improved skin health. For example, one agent capable of increasing sphingomyelinase activity can be used in combination with a second agent capable of decreasing ceramidase activity. Preferably, in order not to decrease the overall effectiveness of the combination of agents, the agent utilized to increase sphingomyelinase activity would not also significantly increase ceramidase activity and the agent utilized to decrease ceramidase activity would not significantly decrease sphingomyelinase activity. In one embodiment, for example, *Chlorella*, which has been shown to increase sphingomyelinase activity by more than about 400% based on the SAST Sphingomyelinase Activity Screening Test and has been shown to have no effect on ceramidase activity based on the CAST Ceramidase Activity Screening Test could be combined with Ceramide Complex CLR, which has been shown to decrease ceramidase activity by more than about 90% based on the CAST Ceramidase Activity Screening Test while not significantly effecting sphingomyelinase activity based on the SAST Sphingomyelinase Activity Screening Test.

In a still further embodiment of the present invention, the agents described herein for increasing the activity of sphingomyelinase or decreasing the activity of ceramidase can be utilized in combination with an organic or inorganic cofactor which is also capable of increasing the activity of sphingomyelinase to produce an increased amount of ceramides. Examples of suitable organic cofactors for use in combination with the agents described herein for increasing the activity of sphingomyelinase include reduced glutathione and yeast extracts such as *Schizosaccharomyces*, *Lipomyces*, and

Saccharomyces. Suitable inorganic cofactors include magnesium. When present on a dry wipe substrate or on an absorbent product in combination with an agent capable of increasing the activity of sphingomyelinase, the cofactor is present in an amount of from about 0.01% (by weight of the treated substrate or product) to about 10% (by weight of the treated substrate or product), preferably from about 0.01% (by weight of the treated substrate or product) to about 1% (by weight of the treated substrate or product). When present as part of the liquid formulation of a wet wipe in combination with an agent capable of increasing the activity of sphingomyelinase, the cofactor is present in an amount of from about 0.01% (by total weight of the liquid formulation) to about 10% (by total weight of the liquid formulation), more preferably from about 0.01% (by total weight of the liquid formulation) to about 1% (by total weight of the liquid formulation).

The present invention is illustrated by the following example which is merely for the purpose of illustration and is not to be regarded as limiting the scope of the invention or manner in which it may be practiced.

EXAMPLE 1

In this Example, botanical extracts and other compounds were tested to determine what effect each compound had on sphingomyelinase activity according to the Sphingomyelinase Activity Screening Test set forth herein and on ceramidase activity according to the Ceramidase Activity Screening Test set forth herein.

Each of the compounds tested, the company where the compound was purchased, the product number of the compound, and the physical form of the compound are set forth in Table 1.

Table 1:

Compound	Company	Product Number	Physical Form
Sedaplant Richter	Chemisches Laboratorium, Berlin	732384	Aqueous
Chlorella	Bio-botanica, Hauppauge, NY	951289	Aqueous
Hexaplant Richter	Chemisches Laboratorium, Berlin	732431	Aqueous
Lavender	Gattefosse, Cedex, France	21189	Aqueous
Marigold (Calendula)	Bell Flavors & Fragrances, Inc. Northbrook, Illinois	62565	Aqueous
Gotu Kola PE 4:1	Bio-botanica, Hauppauge, NY	980657	Powder
Spirulina	Bio-botanica, Hauppauge, NY	951288	Aqueous
Chamonile CL	Dragoco, Totowa, NJ	2/033026	Aqueous
Harpagophytum (Devil's Claw)	Indena- International Sourcing, Uppersaddle River, NJ	EG522	Aqueous
Dragoderma	Dragoco, Totowa NJ	1012550	Aqueous
Phytoplenolin	Bio-botanica, Hauppauge, NY	980510	Aqueous

Aloe Ferox HS	Alban Muller International, Northvale, NJ	7114158	Oil
Sea Parsley Extract	Phillip Rocklel	R10418	Aqueous
Butcher's Broom HS	Alban Muller International, Northvale, NJ	8025951	Aqueous
American Ginseng	Bio-botanica, Hauppauge, NY	9865	Aqueous
Microat afa Complex	Nurture Inc. Missoula, MT	970512-06	Aqueous
Actiphyte of Japanese Green Tea Conc.	Active Organics, Dallas, Tx	300230-94	Liquid
Arnica Oil CLR	Chemisches Laboratorium, Berlin	732407	Oil
Brazil Nut Oil	Croda, Parsippany, NJ	BR2-1004	Oil
Safflower Oil	Arista Industries, Darien, Ct	33767	Oil
Olive Oil	Croda, Parsippany, NJ	OL2-175	Oil
Evening Primrose Oil	Croda, Parsippany, NJ	IPH1-1059	Oil
Ceramide Complex CLR (P)	Chemisches Laboratorium, Berlin	732207	Aqueous
Carrot Oil CLR	Chemisches Laboratorium, Berlin	832526	Oil

Calundula Oil CLR	Chemisches Laboratorium, Berlin	832622	Oil
Apricot Kernel Oil	Croda, Parsippany, NJ	AP-167	Oil
St. John's Wort Oil CLR	Chemisches Laboratorium, Berlin	732208	Oil
Green Tea HS- Chilowt	Alban Muller, Montreuil Cedex, France	12373-00	Aqueous
Biodynes TRF (Yeast Extract)	Brooks Industries, South Plainfield, NJ	39656	Aqueous
Comfrey Leaves Extract	Bell Flavors & Frangrance, Northbrook, Il.	Req:062565	Aqueous
Aloe Gel 1:1 decolorized	Tri-K Industries, Northvale, NJ		Aqueous
Dl-alpha- Tocophenyl Acetate	Rocke Chem.		Aqueous
Borage Oil	Arista Industries, Darien, CT		Oil
Hydrolyzed Soy Protein	Croda, Parsippany, NJ	Hydrosoy 2000SA	Aqueous
MPC-Milk Peptide Complex	Chemisches Laboratorium, Berlin	832641	Powder
Hydrolyzed Whole Oats	Croda, Parsippany, NJ	Cromoist O- 25	Aqueous

Hydrolyzed Elastin	Croda, Parsippany, NJ	Crolastin	Aqueous
MAP, Potassium Laureth Phosphate, (0.2% in PBS)	Rhodia, Cranbury, NJ		Aqueous
Mackeleen EN-77, Sunflower Seedaminopropyl Morpholine Lactate, (0.25% in PBS)	Mcintyre Group, University Park, Il.	EN-77	Aqueous
Tween 20 (0.1% in PBS)	Sigma Chemical, St. Louis, Mo		Aqueous
Sunflower Oil	Croda, Parsippany, NJ	SN2-104	Oil
Avocado Oil CLR	Chemisches Laboratorium, Berlin	832601	Oil
Glycoderm	CLR Chemisches Laboratorium, Berlin, Germany	GLYCODERM (P)	Aqueous

Sphingomyelinase Activity Screening Test

Each of the above-noted compounds was tested for its ability to increase the activity of sphingomyelinase. Each
5 compound was prepared as a testing solution in the same manner as set forth herein.

Step 1: Preparation of Testing Solution Comprising Sphingomyelinase, Sphingomyelin, and Test Compound: A 100
10 microliter test solution was prepared by combining the following: (1) 10 microliters of test compound (if test compound was a powder, a 10 microliter solution of a 0.1 microgram/milliliter solution was prepared by dissolving the

appropriate amount of powder in Phosphate Buffered Saline, pH = 7.4 (VWR, West Chester, Pa); (2) 10 microliters of a 0.1 microgram/milliliter sphingomyelinase (Sigma Chemical, St. Louis, Mo.) in Phosphate Buffered Saline, pH = 7.4, solution;
5 (3) 10 microliters of a 250 microgram/milliliter BODIPY C5 Sphingomyelin (Bodipy FL C5 Sphingomyelin, Molecular Probes, Eugene Or.) in Phosphate Buffered Saline, pH = 7.4, solution; and (4) 70 microliters of Phosphate Buffered Saline, pH = 7.4.

10 Step 2: Preparation of Control Testing Solution
 Comprising Sphingomyelinase and Sphingomyelin: A 100 microliter test solution was prepared by combining the following: (1) 10 microliters of a 0.1 microgram/milliliter sphingomyelinase in Phosphate Buffered Saline, pH = 7.4,
15 solution; (2) 10 microliters of a 250 microgram/milliliter BODIPY FL C5 Sphingomyelin in Phosphate Buffered Saline, pH = 7.4, solution; and (3) 80 microliters of Phosphate Buffered Saline, pH = 7.4.

 Step 3: Preparation of Control Testing Solution
20 Comprising Sphingomyelin: A 100 microliter test solution was prepared by combining the following: (1) 10 microliters of a 250 microgram/milliliter BODIPY FL C5 Sphingomyelin in Phosphate Buffered Saline, pH = 7.4, solution; and (2) 90 microliters of Phosphate Buffered Saline, pH = 7.4.

25 Step 4: Preparation of Control Testing Solution
 Comprising Test Compound and Sphingomyelin: A 100 microliter test solution was prepared by combining the following: (1) 10 microliters of test compound (if test compound was a powder, a 10 microliter solution of a 0.1
30 microgram/milliliter solution was prepared by dissolving the appropriate amount of powder in Phosphate Buffered Saline, pH = 7.4 (2) 10 microliters of a 250 microgram/milliliter BODIPY FL C5 Sphingomyelin in Phosphate Buffered Saline, pH = 7.4,

solution; and (3) 80 microliters of Phosphate Buffered Saline, pH = 7.4.

Assay:

Step 1: Each test solution was shaken for 30 minutes on a laboratory shaker at 25°C to thoroughly mix each testing solution and allow chemical interaction and reaction between the testing mixture components.

Step 2: 1 milliliter of a 2:1 (by volume) mixture of chloroform:methanol was added to each testing solution to stop the chemical reactions. After the addition of the chloroform:methanol mixture, each of the testing solution was vortexed for a period of time of about 1 minute to ensure that the chloroform:methanol mixture was thoroughly distributed throughout the testing mixture.

Step 3: 0.8 milliliters of solution was removed from the organic phase of each testing solution and introduced into a thin layer chromatography vial for further analysis.

Thin Layer Chromatography Procedure:

Step 1: 5 microliters of a testing solution was introduced onto a thin layer chromatography silica gel 60 plate (MERCK, Darmstadt, Germany). The spotting of the testing solution was done with a CAMAG Auto TLC Sampler 4 (Muttenez, Switzerland).

Step 2: Each testing solution was developed by introducing a 90:20:0.5 (by volume) chloroform:methanol:ammonium hydroxide mixture onto each plate and allowing the mixture to run to a length of 3 centimeters.

Step 3: Each band was quantified with an Alpha Innotech Flourchem Plate Imaging System (San Leandro, California). Each plate contained a maximum of ten testing samples including three positive control samples and one negative control sample. The plates were imaged by illuminating with a UV light source (364 nm) and a digital image was taken

through a 585 nm barrier filter with the Flourchem Imager. All fluorescent bands were analyzed using the Flourchem image analysis software and the brightness for each band determined. The Flourchem software determined the Integrated Density Value (IDV) and the Area (pixels) for each fluorescent band. Brightness was then determined from these values. To calculate the effect of the compounds on enzyme activity, the negative control brightness was first subtracted from all of the samples. Then the test compound band on a plate was divided by the average value of the three positive control bands for the same plate. A value above 1 indicates a sphingomyelinase enhancer and a value below 1 indicates an inhibitor.

15 Ceramidase Activity Screening Test

Each of the above-noted compounds was also tested for its ability to decrease the activity of ceramidase. Each compound was prepared as a testing solution in the same manner as set forth herein.

20 Preparation of Testing Solutions:

Step 1: Preparation of Testing Solution Comprising Ceramidase (Fecal Extract), Agent, and Ceramide: A 100 microliter test solution was prepared by combining the following: (1) 10 microliters of test compound (if test compound was a powder, 10 microliters of a 0.1 microgram/milliliter solution was prepared by dissolving the appropriate amount of solid in Phosphate Buffered Saline, pH = 7.4); (2) 10 microliters of infant fecal extract in Phosphate Buffered Saline, pH = 7.4; (3) 10 microliters of 250 microgram/milliliter C5 ceramide in Phosphate Buffered Saline, pH = 7.4; and (4) 70 microliters of Phosphate Buffered Saline, pH = 7.4.

Step 2: Preparation of Control Testing Solution Comprising Ceramidase and Ceramide: A 100 microliter test

solution was prepared by combining the following: (1) 10 microliters of infant fecal extract in Phosphate Buffered Saline, pH = 7.4; (2) 10 microliters of 250 microgram/milliliter C5 ceramide in Phosphate Buffered Saline, pH = 7.4; and (3) 80 microliters of Phosphate Buffered Saline, pH = 7.4.

Step 3: Preparation of Control Testing Solution

Comprising Ceramide: A 100 microliter test solution was prepared by combining the following: (1) 10 microliters of 250 microgram/milliliter C5 ceramide in Phosphate Buffered Saline, pH = 7.4; and (2) 90 microliters of Phosphate Buffered Saline, pH = 7.4.

Assay:

Step 1: Each testing solution was allowed to remain static at 25°C for 18 hours to allow interaction and reaction between the Testing Solution components.

Step 2: 200 microliters of a 2:1 (by volume) mixture of chloroform:methanol was added to each testing solution to stop the chemical reactions. After the addition of the chloroform:methanol mixture, each of the testing solutions was vortexed for a period of time of 1 minute to ensure that the chloroform:methanol mixture was thoroughly distributed throughout the testing mixture.

Step 3: 0.8 milliliters of solution was removed from the organic phase of each testing solution and introduce the removed solution into a thin layer chromatography vial for further analysis.

Thin Layer Chromatography Procedure:

Step 1: 10 microliters of a testing solution was introduced onto a high performance thin layer chromatography silica gel 60 plate.

Step 2: Each testing solution was developed by introducing a 90:20:0.5 (by volume) chloroform:methanol:ammonium hydroxide mixture onto each

plate and allowing the mixture to run to a length of 8 centimeters.

Step 3: Each band was quantified with an Alph Innotech Flourchem Plate Imaging System (or similar system) as discussed above.

The results of these experiments are set forth in Table 2.

Table 2:

Compound	Effect on Sphingomyelinase Activity	Effect on Ceramidase Activity
Sedeplant Richter	7.6 Times Activity	≥ 1 Times Activity
Chlorella	7.1 Times Activity	No Effect
Hexaplant Richter	6.6 Times Activity	≥ 1 Times Activity
Lavender	6.4 Times Activity	No Effect
Marigold (Calendula)	6.4 Times Activity	≥ 1 Times Activity
Gotu Kola PE 4:1	6.2 Times Activity	≥ 1 Times Activity
Spirulina	5.7 Times Activity	No Effect
Chamonile CL	5.1 Times Activity	≥ 1 Times Activity
Harpagophytum (Devil's Claw)	4.9 Times Activity	≥ 1 Times Activity
Dragoderm	4.5 Times Activity	≤ 0.1 Times Activity
Phytoplennolin	4.3 Times Activity	≤ 0.5 Times Activity
Aloe Ferox HS	4.1 Times Activity	≤ 0.5 Times Activity
Sea Parsley Extract	3.4 Times Activity	No Effect
Butcher's Broom HS	3.4 Times Activity	≥ 1 Times Activity
American Ginseng	3.2 Times Activity	≤ 0.5 Times Activity
Microat afa Complex	3.1 Times Activity	≥ 1 Times Activity
Actiphyte of Japanese Green Tea Conc.	2.4 Times Activity	≥ 1 Times Activity
Arnica Oil CLR	1.8 Times Activity	≥ 1 Times Activity
Brazil Nut Oil	1.5 Times Activity	≥ 1 Times Activity
Safflower Oil	No Effect	≥ 1 Times Activity
Olive Oil	No Effect	≥ 1 Times Activity
Evening Primrose Oil	No Effect	≥ 1 Times Activity

Ceramide Complex CLR (P)	No Effect	≤ 0.1 Times Activity	
Carrot Oil CLR	No Effect	≥ 1 Times Activity	
Calundula Oil CLR	No Effect	≥ 1 Times Activity	
Apricot Kernel Oil	No Effect	≥ 1 Times Activity	
St. John's Wort Oil CLR	No Effect	≥ 1 Times Activity	
Green Tea HS-Chilowt	0.8 Times Activity	≤ 0.1 Times Activity	
Biodynes TRF (Yeast Extract)	0.8 Times Activity	No Effect	
Comfrey Leaves Extract	0.7 Times Activity	≤ 0.1 Times Activity	
Aloe Gel 1:1 decolorized	0.7 Times Activity	≤ 0.5 Times Activity	
D1-alpha-Tocophenyl Acetate	0.6 Times Activity	≥ 1 Times Activity	
Borage Oil	0.6 Times Activity	≥ 1 Times Activity	
Hydrolyzed Soy Protein	0.6 Times Activity	≤ 0.1 Times Activity	
MPC-Milk Peptide Complex	0.4 Times Activity	No Effect	
Hydrolyzed Whole Oats	0.3 Times Activity	≥ 1 Times Activity	
Hydrolyzed Elastin	0.2 Times Activity	No Effect	
MAP, Potassium Laureth Phosphate, (0.2% in PBS)	0.1 Times Activity	No Effect	
Mackeleen EN-77, Sunflower Seedaminopropyl Morpholine Lactate, (0.25% in PBS)	0.1 Times Activity	No Effect	
Tween 20 (0.1% in PBS)	0.1 Times Activity	No Effect	
Sunflower Oil	No Effect	≥ 1 Times Activity	
Avocado Oil CLR	No Effect	≥ 1 Times Activity	
Glycoderm	No Effect	≤ 0.1 Times Activity	

As the data set forth in Table 2 indicate, several compounds tested exhibited the ability to increase sphingomyelinase activity and/or decrease ceramidase activity. Notably, Dragoderin, Phytoplenolin, Aloe Ferox HS, and American Ginseng are highly preferred agents as they all not only increase the activity of sphingomyelinase, but also decrease the activity of ceramidase.

In view of the above, it will be seen that the several objects of the invention are achieved. As various changes could be made in the above-described products and methods without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense.

WHAT IS CLAIMED IS:

1. A wipe for improving skin health comprising a fibrous wipe substrate and a sphingomyelinase activity increasing agent for increasing sphingomyelinase activity for the production of ceramides by at least about 100%.
2. The wipe as set forth in claim 1 wherein the sphingomyelinase activity increasing agent is for increasing sphingomyelinase activity by at least about 100% as determined by a SAST Sphingomyelinase Activity Screening
5 Test.
3. The wipe as set forth in claim 1 wherein the agent is selected from the group consisting of Sedaplant Richter, Chlorella, Hexaplant Richter, Lavender, Marigold (Calendula), Gotu Kola PE 4:1, Spirulina, Chamonile CL, Harpagophytum
5 (Devil's Claw), Dragoderm, Phytoplentin, Aloe Ferox HS, Sea Parsley Extract, Butcher's Broom HS, American Ginseng, Microat Afa Complex, and Actiphyte of Japanese Green Tea Conc.
4. The wipe as set forth in claim 3 wherein the agent is selected from the group consisting of Sedaplant Richter, Chlorella, Hexaplant Richter, Lavender, Marigold (Calendula), and Gotu Kola PE 4:1.
5. The wipe as set forth in claim 3 wherein the agent is Dragoderm.
6. The wipe as set forth in claim 1 wherein the agent increases the sphingomyelinase activity by at least about 200%.

7. The wipe as set forth in claim 1 wherein the agent increases the sphingomyelinase activity by at least about 400%.

8. The wipe as set forth in claim 1 wherein the wipe is a dry wipe and the agent is present in an amount of from about 0.01% (by weight of the treated substrate) to about 50% (by weight of the treated substrate).

9. The wipe as set forth in claim 1 wherein the wipe is a wet wipe and further comprises a liquid formulation, said agent being present in an amount of from about 0.01% (by total weight of the liquid formulation) to about 50% (by total weight of the liquid formulation).

10. The wipe as set forth in claim 1 further comprising a cofactor selected from the group consisting of reduced glutathione, *Schizosaccharomyces*, *Lipomyces*, *Saccharomyces*, and magnesium.

11. A wipe for improving skin health comprising a fibrous wipe substrate and a ceramidase activity decreasing agent for decreasing ceramidase activity by at least about 50%.

12. The wipe as set forth in claim 11 wherein the ceramidase activity decreasing agent is for decreasing ceramidase activity by at least about 50% as determined by a CAST Ceramidase Activity Screening Test.

13. The wipe as set forth in claim 11 wherein the ceramidase activity is decreased by at least about 75%.

14. The wipe as set forth in claim 11 wherein the ceramidase activity is decreased by at least about 90%.

15. The wipe as set forth in claim 11 wherein the agent is selected from the group consisting of Dragoderm, Ceramide Complex CLR (P), Green Tea HS-Chilowt, Comfrey Leaves Extract, Hydrolyzed Soy Protein, and Glycoderm.

16. The wipe as set forth in claim 11 wherein the wipe is a dry wipe and the agent is present in an amount of from about 0.1% (by weight of the treated substrate) to about 50% (by weight of the treated substrate).

17. The wipe as set forth in claim 11 wherein the wipe is a wet wipe and further comprises a liquid formulation, said agent being present in an amount of from about 0.01% (by total weight of the liquid formulation) to about 50% (by
5 total weight of the liquid formulation).

18. A wipe comprising a fibrous wipe substrate and a sphingomyelinase activity increasing agent for increasing sphingomyelinase activity for the production of ceramides by at least about 100% and a ceramidase activity decreasing
5 agent for decreasing ceramidase activity by at least 50%.

19. The wipe as set forth in claim 18 wherein the agent is Dragoderm.

20. A product for improving skin health comprising an absorbent substrate and a sphingomyelinase activity increasing agent for increasing sphingomyelinase activity for the production of ceramides by at least about 100%.

21. The product as set forth in claim 20 wherein the sphingomyelinase activity increasing agent is for increasing sphingomyelinase activity by at least about 100% as determined by a SAST Sphingomyelinase Activity Screening Test.

22. The product as set forth in claim 20 wherein the agent is selected from the group consisting of Sedaplant Richter, Chlorella, Hexaplant Richter, Lavender, Marigold (Calendula), Gotu Kola PE 4:1, Spirulina, Chamomile CL, Harpagophytum (Devil's Claw), Dragoderin, Phytoplenolin, Aloe Ferox HS, Sea Parsley Extract, Butcher's Broom HS, American Ginseng, Microat Afa Complex, and Actiphyte of Japanese Green Tea Conc.

23. The product as set forth in claim 20 wherein the agent is selected from the group consisting of Sedaplant Richter, Chlorella, Hexaplant Richter, Lavender, Marigold (Calendula), and Gotu Kola PE 4:1.

24. The product as set forth in claim 20 wherein the agent increases the sphingomyelinase activity by at least about 200%.

25. The product as set forth in claim 20 wherein the agent increases the sphingomyelinase activity by at least about 400%.

26. The product as set forth in claim 20 wherein the agent is present in an amount of from about 0.01% (by weight of the treated product) to about 50% (by weight of the treated product).

27. The product as set forth in claim 20 wherein the product is selected from the group consisting of a diaper, training pants, adult incontinence garments, feminine napkins, paper towels, tampons, breast pads, interlabial
5 pads, facial tissue, wound management products, and bath tissue.

28. The product as set forth in claim 20 further comprising a cofactor selected from the group consisting of reduced glutathione, *Schizosaccharomyces*, *Lipomyces*, *Saccharomyces*, and magnesium.

29. A product for improving skin health comprising an absorbent substrate and a ceramidase activity decreasing agent for decreasing ceramidase activity by at least about 50%.

30. The product as set forth in claim 29 wherein the ceramidase activity decreasing agent is for decreasing ceramidase activity by at least about 50% as determined by a CAST Ceramidase Activity Screening Test.

31. The product as set forth in claim 29 wherein the agent is capable of decreasing the ceramidase activity by at least about 75%.

32. The product as set forth in claim 29 wherein the agent is capable of decreasing the ceramidase activity by at least about 90%.

33. The product as set forth in claim 29 wherein the agent is selected from the group consisting of Dragoderm, Ceramide Complex CLR (P), Green Tea HS-Chilowt, Comfrey Leaves Extract, Hydrolyzed Soy Protein, and Glycoderm.

34. The product as set forth in claim 29 wherein the agent is present in an amount of from about 0.1% (by weight of the treated substrate) to about 50% (by weight of the treated substrate).

35. The product as set forth in claim 29 wherein the agent is Dragoderm.

36. The product as set forth in claim 29 wherein the product is selected from the group consisting of a diaper, training pants, adult incontinence garments, feminine napkins, paper towels, tampons, breast pads, interlabial
5 pads, facial tissue, wound management products, and bath tissue.

37. A product for improving skin health comprising an absorbent substrate and a sphingomyelinase activity increasing agent for increasing sphingomyelinase activity for the production of ceramides by at least about 100% and a
5 ceramidase activity decreasing agent for decreasing ceramidase activity by at least about 50%.

38. The product as set forth in claim 37 wherein the sphingomyelinase activity increasing agent is for increasing sphingomyelinase activity by at least about 100% as determined by a SAST Sphingomyelinase Activity Screening Test
5 and the ceramidase activity decreasing agent is for decreasing ceramidase activity by at least about 50% as determined by a CAST Ceramidase Activity Screening Test.

39. A method for increasing the intracellular concentration of ceramides, the method comprising contacting skin with a sphingomyelinase activity increasing agent for

increasing sphingomyelinase activity for the production of
5 ceramides by at least about 100%.

40. The method as set forth in claim 39 wherein the
sphingomyelinase activity increasing agent is for increasing
sphingomyelinase activity by at least about 100% as
determined by a SAST Sphingomyelinase Activity Screening
5 Test.

41. The method as set forth in claim 39 wherein the
agent is contained in a personal care product.

42. The method as set forth in claim 39 wherein the
personal care product is selected from the group consisting
of wet wipes, dry wipes, diapers, tampons, breast pads,
feminine napkins, interlabial pads, facial tissue, bath
5 tissue, and paper towels.

43. The method as set forth in claim 39 wherein the
agent is selected from the group consisting of Sedaplant
Richter, Chlorella, Hexaplant Richter, Lavender, Marigold
(Calendula), Gotu Kola PE 4:1, Spirulina, Chamonile CL,
5 Harpagophytum (Devil's Claw), Dragoderma, Phytoplentin, Aloe
Ferox HS, Sea Parsley Extract, Butcher's Broom HS, American
Ginseng, Microat Afa Complex, and Actiphyte of Japanese Green
Tea Conc.

44. The method as set forth in claim 43 wherein the
agent is selected from the group consisting of Sedaplant
Richter, Chlorella, Hexaplant Richter, Lavender, Marigold
(Calendula), and Gotu Kola PE 4:1.

45. The method as set forth in claim 43 wherein the
agent is Dragoderma.

46. A method for decreasing the activity of ceramidase on skin, the method comprising contacting skin with a ceramidase activity decreasing agent for decreasing ceramidase activity by at least about 50%.

47. The method as set forth in claim 46 wherein the ceramidase activity decreasing agent is for decreasing ceramidase activity by at least about 50% as determined by a CAST Ceramidase Activity Screening Test.

48. The method as set forth in claim 40 wherein the agent is selected from the group consisting of Dragoderm, Ceramide Complex CLR (P), Green Tea HS-Chilowt, Comfrey Leaves Extract, Hydrolyzed Soy Protein, and Glycoderm.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/13489

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 338 855 B1 (ALBACARYS ET AL.) 15 January 2002 (2002-01-15) claim 1 column 2, line 48 - line 54 column 4, line 61 - line 65 column 6, line 20 - line 50 column 8, line 32 - line 34 column 18, line 58 column 20, line 19 column 21, line 50 - line 67 column 22, lines 10,23,24,64 column 23, line 15 - line 16 column 25, line 37 - line 38 column 26, line 59 column 32, line 47 - line 48	1-4, 6-10,18, 20-28, 37,38
Y	----- -/-	3,22,42

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 August 2003

Date of mailing of the international search report

09. 01. 2004

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/13489

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/136755 A1 (TYRRELL ET AL.) 26 September 2002 (2002-09-26) claims 1,5,9,20,25,29 paragraphs [0018], [0025], [0034], [0044], [0057], [0116], [0117], [0120] - [0122]	1-4,6,7, 9,10,18, 20-28, 37,38
X	US 6 159 487 A (ZNAIDEN ET AL.) 12 December 2000 (2000-12-12) claims 1,2 column 2, line 65 - line 67 column 3, lines 20,51,58 column 4, lines 4,34 tables I-IV	1-4,6,7, 9,10,18, 20-25, 27,28
X	WO 99/36032 A (LAVIPHARM LABORATORIES INC.) 22 July 1999 (1999-07-22) claims 1,3,7,8 page 9, line 20 - line 21	1-4,6,7, 9,20-27
X	US 6 187 728 B1 (MCMANUS) 13 February 2001 (2001-02-13) claims 1,2 figures 2A,2B column 4, line 29 - line 37 column 10, line 46 - line 60 column 11, line 6 - line 11 examples 1,2	20-26, 37,38
Y	WO 01/095728 A (FD MANAGEMENT INC) 20 December 2001 (2001-12-20) claims 1,8	3,22
Y	US 2002/015743 A1 (MEYBECK ET AL.) 7 February 2002 (2002-02-07) example 6	3,22
Y	US 5 215 759 A (MAUSNER) 1 June 1993 (1993-06-01) claim 11; table III	3,22
X	WO 99/62478 A (BEIERSDORF AG ET AL.) 9 December 1999 (1999-12-09) claims 1,2 examples 1,2,6 page 5, last paragraph - page 6, paragraph 1 -/--	39-41,43

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/13489

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI Week 200020 Derwent Publications Ltd., London, GB; AN 2000-232904 [20] XP002252408 & JP 2000 053533 A (PIAS KK) 22 February 2000 (2000-02-22) abstract</p>	39-41,43
Y	<p>-----</p>	42

INTERNATIONAL SEARCH REPORT

national application No.
 PCT/US 03/13489

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-10, 18-28, 37-45

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: -

The following statement makes reference to the set of claims for which a search has been carried out, see form PCT/ISA/206 (extra sheet).

Present claims 1,2 6-10, 18, 20,21 24-28, 37-42 relate to products defined by reference to a desirable characteristic, namely that they comprise a "sphingomyelinase activity increasing agent".

In the case of claims 18, 37 and 38 a further desirable characteristic of the claimed products is that they comprise a "ceramidase activity decreasing agent".

The claims cover all products having this characteristic, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products containing as "sphingomyelinase activity increasing agent" one or more of the agents described in page 13, line 34 - page 14, line 7; which are also listed in page 30, table 2 from "Sedepiant Richter" up to "Brazil nut" and claimed in claims 3-5, 22, 23 and 43-45. The search has been carried out as well for products containing additionally, as "ceramidase activity decreasing agent", the agents described in page 18, lines 11-15

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10 18-28 37-45

A wipe for improving skin health comprising a fibrous substrate and a sphingomyelinase activity increasing agent.

A wipe for improving skin health comprising a fibrous substrate and a sphingomyelinase activity increasing agent and a ceramidase activity decreasing agent.

A product for improving skin health comprising an absorbent substrate and a sphingomyelinase activity increasing agent.

A product for improving skin health comprising an absorbent substrate and a sphingomyelinase activity increasing agent and a ceramidase activity decreasing agent.

A method for increasing the intracellular concentration of ceramides comprising contacting the skin with a sphingomyelinase activity increasing agent.

2. claims: 11-17 29-36 46-48

A wipe for improving skin health comprising a fibrous substrate and a ceramidase activity decreasing agent.

A product for improving skin health comprising an absorbent substrate and a ceramidase activity decreasing agent.

A method for decreasing the activity of ceramidase on skin comprising contacting the skin with a ceramidase activity decreasing agent.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. The present invention relates to a method of
determining the optimal location for a new
facility, such as a warehouse or a distribution
center, based on the location of existing
facilities and the demand for the goods
being distributed.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/13489

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INTERNATIONAL SEARCH REPORT

International Application No

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